Use of antibiotic-loaded polymethylmethacrylate beads for the treatment of extracavitary prosthetic vascular graft infections

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Purpose: **This study was conducted to assess the efficacy of antibiotic-loaded polymethylmethacrylate (PMMA) beads in the management of lower extremity extracavitary prosthetic arterial graft infection.**

Methods: **This was a retrospective review of 34 patients treated for vascular surgical site (VSS) infections involving 36 prosthetic lower extremity arterial bypasses using antibiotic-loaded PMMA beads and culture-specific parenteral antibiotics for 4 to 6 weeks. Sites of graft infection were explored, debrided, and cultured. As determined from the results of Gram's stains of VSS purulence, PMMA powder was polymerized with an antibiotic (vancomycin, daptomycin, or tobramycin/gentamicin, or a combination), molded into a chain of beads, and implanted adjacent to the infected graft after debridement and pulsed-spray antibacterial lavage. All wounds were closed primarily with planned exploration to verify sterilization before a graft preservation or in situ replacement procedure. Treatment outcomes, including wound sterilization, were analyzed based on tissue culture isolates, procedures for persistent infection, and freedom from graft infection.**

Results: **Cultures isolated 42 pathogens, (32 gram-positive, 9 gram-negative, 1 *Candida albicans*) with methicillin-resistant *Staphylococcus aureus* (MRSA) cultured from 16 (44%) of 36 surgical site infections. As determined from the initial operative Gram's stain or a prior culture result, vancomycin PMMA beads were implanted in 29 of 36 VSS infections at the first procedure; daptomycin (n = 4) or tobramycin (n = 3) beads were implanted in the rest. Repeat VSS exploration and culture results led to an average of 2.5 antibiotic bead replacements before definitive treatment. A sterile (no growth on tissue culture) VSS was achieved in 87% of cases before a graft preservation (n = 16) or in-situ replacement of an infected graft (n = 20) procedure. No patient deaths occurred. Early and late limb salvage was 100%. Infection recurred in 4 (11%) VSSs during a mean 23-month follow-up period, one within 3 months owing to unrecognized bowel injury associated with in situ replacement of an aortofemoral graft limb.**

Conclusion: **Antibiotic-loaded PMMA beads may be a useful adjunct in the contemporary surgical management of VSS infection involving a prosthetic graft. Wound sterilization was achieved in most VSSs before graft preservation or an in-situ replacement procedure, including infections caused by MRSA, a pathogen isolated in half of the extracavitary prosthetic graft infections. This preliminary trial shows the potential benefit of this new technique, but further study is required to prove efficacy. (J Vasc Surg 2006;44:757-61.)**

Infection involving a prosthetic arterial graft presenting either early (<3 months) or later can result in significant patient morbidity and mortality. Traditional management of this vascular complication has stressed the importance of intravenous administration of culture-specific antibiotics with concomitant graft excision and extra-anatomic bypass in cases of inadequate collateral circulation.[1-3] Other vascular groups have successfully used in-situ replacement, with or without autologous vein grafts, and in selected patients with an early prosthetic graft infection, graft preservation is possible.[4-6] Failure of these procedures is most commonly due to persistent vascular surgical site (VSS) infection. To achieve a sterile wound, most vascular surgeons have relied on povidone iodine wound irrigation systems, serial wound debridements, and muscle flap coverage of the preserved graft alone or in conjunction with an in situ graft replacement procedure.[6-9]

The clinical application of antibiotic-loaded polymethylmethacrylate (PMMA) cement has been primarily by orthopedic surgeons as an adjunct for the treatment of tibial osteomyelitis or prosthetic joint infection.[10,11] The efficacy of local antibiotic delivery systems, in the form of antibiotic-loaded PMMA beads, has also been shown in reports on the management of complicated diabetic foot infections and in preventing infection of ventricular assist devices.[12,13] Data on antibiotic bead usage for treating VSS infections are limited and consist of small clinical series using a variety of techniques, including permanent implantation.[14] During the past 5 years, our vascular group has used antibiotic-loaded PMMA beads to deliver high drug concentrations in VSSs during the initial management of a prosthetic graft infection. The goal of antibiotic bead placement is to sterilize the VSS and thus improve the safety and

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Table I. Clinical presenting signs of 25 early and 11 late appearing vascular surgical sites with extracavitary prosthetic graft infection

Presenting sign	*Early infection <3 months*	*Late infection >3 months*
Wound infection	14	—
Pseudoaneurysm	1	—
Infected hematoma	3	—
Abscess	3	8
Groin sinus tract	—	2
Infected lymphocele	4	1

success of a subsequent in situ graft replacement or graft preservation procedures.

PATIENTS AND METHODS

Patient population. A query of our vascular registry identified 34 patients with 36 lower extremity extracavitary prosthetic graft infection sites in which antibiotic-loaded PMMA beads were implanted at the time of VSS exploration to confirm and treat infection. Use of antibiotic beads began in 2001, and only patients with >3-months of follow-up were included. The criteria for antibiotic bead usage were clinical signs of infection involving an extracavitary prosthetic graft implant site, including purulent wound fluid, or positive Gram's stain of perigraft fluid or tissue, or both. Early (<3-month) graft infections met criteria of the Szilagyi type III prosthetic vascular graft infection (ie, wound infection involving the graft). Patients treated by emergent excision of an infected prosthetic graft were excluded from analysis. These consecutive patients (20 men, 14 women) were primarily treated by one author (D. F. B), with other faculty vascular surgeons (M. R. B., B. L. J., M. L. S.) participating in antibiotic bead exchange and wound debridement procedures. The mean patient age was 68.5 years (range, 47 to 89 years).

The presenting clinical manifestations of 25 early and 11 late VSS infections are shown in Table I. Most of the infections (32 of 36) presented as a groin wound infection and the remaining sites involved the entire infrainguinal prosthetic bypass. All patients were initially prescribed broad-spectrum parenteral antibiotics with subsequent changes determined by wound and graft culture results and susceptibility testing. After hospital discharge, all patients received parenteral or oral culture-specific antibiotics for a minimum of 6 weeks.

The types of prosthetic graft infections treated included the extracavitary segment of an aortofemoral graft limb in 16, polytetrafluoroethylene (PTFE) femorofemoral graft in 6, PTFE axillofemoral graft–groin segment in 1, infrainguinal PTFE bypass in 11, and 2 multigraft infections (PTFE femorofemoral and infrainguinal bypass, and polyester aortobifemoral with PTFE infrainguinal bypass). Two patients presented with bilateral groin wound infections after polyester aortobifemoral bypass. One patient required emergent treatment owing to pseudoaneurysm hemorrhage of a femoral interposition graft and underwent PTFE in situ graft replacement with antibiotic bead implant as a bridge procedure prior to staged deep femoral vein replacement. All other procedures were performed as nonemergent treatment of a VSS infection.

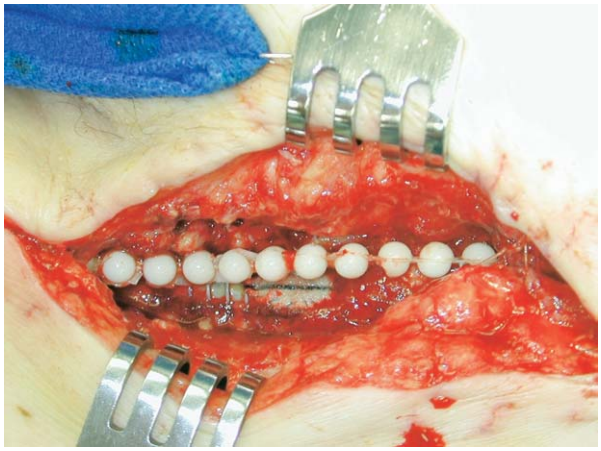

Fig 1. Antibiotic-loaded polymethylmethacrylate beads implanted adjacent to an infected polytetrafluoroethylene graft segment.

Operative technique. Surgical exploration of the surgical site was performed to obtain Gram's stain and culture testing of perigraft tissue and fluid and to confirm involvement of the vascular prosthesis. All necrotic or infected tissue was debrided, followed by pulse lavage irrigation of the VSS using 3 liters of Clorpactin (United-Guardian, Inc, Hauppauge, NY) (oxychlorosene sodium) solution (6 g/3 L).

Antibiotic beads were made in the operating room by using PMMA powder (40 g) polymerized with methacrylate (20 mL) to which vancomycin (2 g) or daptomycin (1 g; Cubist Pharmaceuticals, Lexington, Mass) was added for gram-positive organisms, and an aminoglycoside (tobramycin, 1 g; gentamicin, 1 g) if gram-negative organisms were present. Antibiotic-loaded PMMA cement was placed in a 5-mm bead mold and attached to 2-0 stainless steel. The hardened antibiotic beads were then implanted as a bead-string adjacent to the infected graft segment (Fig 1). Subcutaneous tissue was closed over the graft and beads using absorbable sutures, and when possible, skin was approximated with monofilament nylon sutures.

Typically, the VSS was re-explored 3 days later (range, 3 to 6 days), after culture results were available (Fig 2). The VSS and graft were inspected for invasive infection, tissue cultures were obtained, additional tissue was débrided if necessary, and antibacterial lavage of the VSS was performed. The antibiotic beads were removed and replaced with new antibiotic-loaded PMMA beads according to antibiotic susceptibility testing of the prior VSS culture results. The replaced antibiotic beads were attached to a 0 polypropylene suture and brought out through a separate skin incision to allow removal at bedside.

If the second VSS culture exhibited no growth (ie, was sterile) the implanted antibiotic beads were removed at

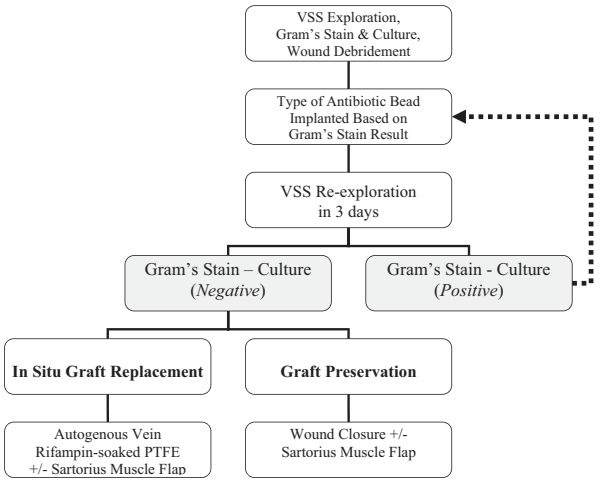

Fig 2. Treatment algorithm for implantation of antibiotic-loaded beads in the vascular surgical sites *(VSS)* with infected prosthetic vascular grafts.

bedside or at the time of definitive treatment, which consisted of graft preservation by wound closure with muscle flap coverage of the prosthetic graft or in situ replacement of involved graft with autologous vein or rifampin-soaked PTFE (Gel-Seal Vascutek, Somerset, NJ) and sartorius muscle flap coverage. If the wound cultures were not sterile at the time of re-exploration, new antibiotic beads were inserted. In some instances, the operating surgeon proceeded with in situ vein replacement at this time and beads were removed 5 to 7 days later. In general, sterile VSS cultures were required before final graft preservation or an in situ prosthetic graft replacement procedure.

Wound sterilization was defined by an absence of bacterial growth by tissue culture in a in VSS with tissue that appeared healthy and viable. Our treatment algorithm was used to complete the surgical intervention. Graft preservation was attempted on all early (<3 month) graft infections with a single bacterial isolate, such as *Staphylococcus aureus*, and segmental graft involvement. For polymicrobial and all late-appearing graft infections, in-situ graft replacement was typically performed. Culture-specific antibiotic treatment was continued for a mean 5.3 weeks (range, 4 to 8 weeks).

RESULTS

Tissue cultures obtained at the initial VSS exploration isolated 43 pathogens (Table II). Methicillin-resistant *S aureus* (MRSA) was cultured from 16 (44%) of the 36 infected graft sites. The initial Gram's stain of perigraft fluid and tissue identified 30 gram-positive VSSs, three gram-negative, and no organisms in three. All patients received PMMA antibiotic-loaded beads at the first operative procedure: vancomycin in 29 VSSs, daptomycin in four, and vancomycin/tobramycin in three. Gram-positive infection was confirmed in 32 (88%) of 36 VSSs, including isolates of MRSA in 16, methicillin-sensitive *S aureus* in 7, *S epidermidis* in 7, enterococcus–*Streptococcus faecalis* in 2, and β-hemolytic *Streptococcus* in 1. Seven gram-negative isolates were cultured, including strains of *Pseudomonas aeruginosa* (n = 5), *Escherichia coli* (n = 2), *Proteus*, and *Morganella* sp. One VSS infection isolated only *Candida albicans*.

Table II. Type and (number) of bacterial and fungal isolates recovered from 36 vascular surgical sites with extracavitary prosthetic graft infection

Type	*N*
Gram-positive	
Methicillin resistant *S. aureus*	16
Methicillin sensitive *S. aureus*	7
S. epidermidis	7
Enterococcus–*S faecalis*	2
β-hemolytic *Streptococcus*	1
Gram-negative	
Pseudomonas sp	5
Escherichia coli	2
Morganella morganii	1
Proteus	1
Other	
Candida albicans	1

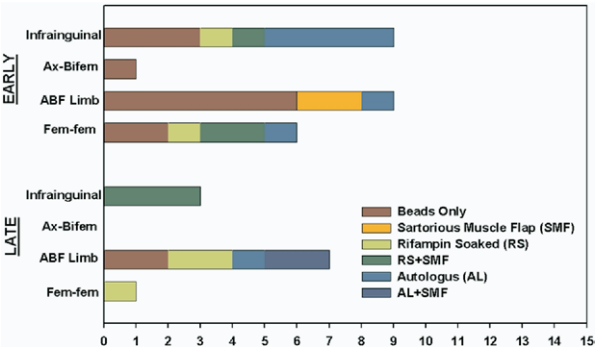

Fig 3. Types of management used to treat 25 early and 11 late-appearing extracavitary prosthetic graft infections. *RS,* Rifampin-soaked polytetrafluoroethylene or polyester gelatin-impregnated graft; *SMF,* sartorius muscle flap; *AL,* autologous vein; *ABF,* aortobifemoral.

The treatments used for 25 early and 11 late extracavitary graft infections are summarized in Fig 3. Graft preservation was performed in 16 VSSs and in situ replacement in 20, with sartorius muscle flap coverage of the graft used in 12 (33%). Wound debridement with antibiotic beads implant was the sole treatment in 10 of 25 early and 2 of 11 late graft infections, and in situ graft replacement was performed in 10 early and 9 late graft infections.

VSS sterilization was achieved after the initial debridement procedure as documented by tissue culture in 18 (58%) of 31 VSSs tested. Five patients did not have cultures and underwent an in situ replacement of the infected graft using autologous vein. Overall, wound sterilization was documented in 27 (87%) of 31 VSSs before graft preserva-

tion (n = 16) or graft replacement (n = 15). Antibiotic beads were replaced a mean of 2.5 times (range, 1 to 4 times).

Outcomes at 30-days included no patient deaths, allergic reactions, or limb loss. One in situ replacement procedure failed owing to an unrecognized small-bowel injury. This required reoperation and bowel repair, and the deep vein replacement of the aortofemoral graft was successful. The average length of hospitalization was 18 days (range, 5 to 56 days).

No patient was lost to follow-up during a mean 23-month postoperative period. At last follow-up, 33 patients had healed VSS without signs or symptoms of infection. Three patients died within 3 months after discharge of causes not directly related to VSS infection or its treatment. One patient with a healing VSS groin wound had cardiopulmonary arrest at home, and the remaining two patients with clinical signs of VSS infection died from cerebrovascular events (stroke, subarachnoid hemorrhage).

Recurrent graft infection developed in four of the 31 surviving patients at a mean time interval of 11 months (range, 6 to 15 months). Pseudoaneurysms occurred in two patients at the treated VSS site at 6 and 12 months and required deep vein replacement of an aortofemoral graft limb for MRSA and *Candida* infection, respectively. One patient presented with recurrent femorofemoral graft infection 15 months after a graft preservation procedure and underwent deep vein replacement of the graft infected by *P aeruginosa*. Two of three patients treated for recurrent VSS infections had persistent positive cultures at the time of their in situ replacement procedure. The last patient treated for recurrent graft infection presented 15 months after in situ replacement of an aortofemoral graft limb with infection proximal to treated VSS owing to a retained, thrombosed aortofemoral graft segment that had not been previously excised. This infected segment was excised, and no involvement with the treated VSS was identified.

DISCUSSION

Management of prosthetic graft infection remains a difficult clinical problem, especially with the emergence of resistant bacterial strains such as MRSA. Vascular surgeons should suspect MRSA infection in patients presenting with both early and late VSS infection. The prevalence of MRSA infection was 44% in this series, similar for extracavitary graft infections presenting early (11 of 25) and late (5 of 11). This incidence is similar to recent audits of vascular infection that reported 53% of *S aureus* infections were methicillin resistant. The overall MRSA vascular surgical site infection rate was 4%. The incidence was higher after infrainguinal procedures than after femorofemoral or aortofemoral bypass grafting.[15] Factors associated with VSS infection included MRSA colonization, a groin implant site, redo procedure, and no MRSA antibiotic prophylaxis. The emergence of MRSA colonization on vascular surgery units with a prevalence of 7% to 8% suggests a change in antibiotic prophylaxis may be appropriate, particularly in patients having prosthetic grafts implanted in the groin.[16]

Patients with extracavitary VSS infection typically present clinical signs in the groin region, with infection involving the femoral segment of an aortofemoral graft limb, an extra-anatomic (femorofemoral, axillofemoral), or infrainguinal prosthetic arterial bypass. Most patients are not septic, and anastomotic hemorrhage is uncommon unless the patient or the surgeon has procrastinated.

Treatment has traditionally involved extra-anatomic bypass with graft excision.[1,17] However, many patients presenting with an extracavitary graft infection have undergone complex arterial repairs and the options for ex-situ revascularization are limited or not possible. These circumstances have prompted vascular surgeons to attempt graft preservation treatment or perform in situ replacement using autologous vein or an antibiotic-impregnated graft.

Calligaro et al[6] reported a 20-year experience using a graft preservation strategy that included serial debridement and povidone-iodine or antibiotic-soaked dressing changes three times daily to sterilize the VSS and promote granulation tissue coverage over exposed bypass grafts.[6] Cited benefits included a simpler method of treatment, decreased amputation rates, and low incidence of graft-related hemorrhage.

In our treatment algorithm, antibiotic beads are used as adjunct to surgical debridement and tissue cleansing to sterilize the VSS and prosthetic graft by providing high drug concentration to adjacent tissues and the biomaterial surfaces. Treatment is done with the VSS wound closed, avoiding the necessity of an exposed arterial graft, intensive care unit monitoring, and multiple daily dressing changes. VSSs are explored every 3 to 5 days to re-evaluate for and treat invasive infection by performing further tissue debridement if necessary, and to obtain tissue culture to determine if perigraft tissue sterilization has been achieved. Once the VSS culture is negative, a graft preservation procedure can be completed, typically by performing muscle flap coverage of the treated graft segment and suturing the wound closed; or in situ replacement of extracavitary graft is performed. This approach ensures that wound closure or an arterial reconstruction is not performed in the setting of an invasive wound infection.

The implantation of antibiotic-loaded PMMA beads was effective in producing a sterile VSS in the presence of a patent, prosthetic arterial bypass. After a single implantation of antibiotic beads, negative tissue cultures were obtained in two thirds of VSSs; and after serial bead exchanges, 87% of VSS were sterile by culture. The benefit of VSS sterilization is based on the hypothesis that a wound with minimal colonization will exhibit less healing problems and thus improve the clinical success of graft preservation or in situ replacement procedures. Our treatment outcomes with antibiotic beads were better that those reported by Calligaro et al[6] and their graft preservation strategy, including 30-day mortality (0% vs 12%), limb loss (0% vs 4%), and wound healing rates (89% vs 71%).[6] Of note, no graft-related hemorrhage occurred in this series.

The incidence of secondary procedures for recurrent graft infection was low. Five (15%) patients developed a

second graft infection requiring intervention, of which four involved the treated VSS. Two were the result of technical error consisting of a small-bowel injury during an in situ replacement procedure, and failure to remove a prior thrombosed aortofemoral graft limb segment. Three recurrent infections involving the treated VSS site, all developed beyond 6-months and were managed by deep vein replacement of the infected prosthetic graft segment. Two patients had persistent positive wound cultures despite antibiotic beads placements at the time of their in situ replacement.

CONCLUSION

The clinical application of antibiotic beads in the management of VSS infection deserves further study. The efficacy of this type of local antibiotic delivery system in treating or preventing infection has been demonstrated in experimental animal models and in clinical applications for the treatment of prosthetic joint infection, tibial osteomyelitis, and diabetic foot infection.[9-11,13] Our vascular group chose not to performed a randomized study with a control group receiving no antibiotic beads, primarily because the number of enrolled subjects required to demonstrate a treatment difference is not feasible at a single institution. Rather, our approach has been to incorporate this treatment adjunct into clinical care in selected patients presenting with VSS infection, and then carefully evaluate outcomes associated with graft preservation or in situ replacement procedures by reporting on factors associated with success or failure of treatment. We believe that attempts to achieve VSS sterilization, including the use of antibiotic beads, is clinically useful and should enhance the safety of caring for patients with extra-cavitary graft infections.

AUTHOR CONTRIBUTIONS

Conception and design: PS, PA, DB, RB, SF, MB, BJ, MS
Analysis and interpretation: PS, PA, DB, RB, SF, MB, BJ, MS
Data collection: PS, PA, RB
Writing the article: PS, PA, DB, RB, SF
Critical revision of the article: PS, DB, PA, SF, MB, BJ, MS
Final approval of the article: PS, PA, DB, RB, SF, MB, BJ, MS
Statistical analysis: SF, PS
Obtained funding: Not applicable
Overall responsibility: PS

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